45. (New) The dosage form according to claim 44, wherein the antidegradation agent is phosphoric acid.

46. (New) The dosage form according to claim 43, wherein the semipermeable membrane further comprises cellulose acetate and a flux-enhancing agent.

47. (New) The dosage form according to claim 46, wherein the flux-enhancing agent is a copolymer of ethylene and propylene oxide.

REMARKS

This amendment is filed in response to the Office Action dated November 8, 2001.

Claims 1-34 are rejected under 35 U.S.C. 103(a) as being obvious over *Dong et al.* (5,770,227) in view of *Patrick et al.* and *Ayer et al.* (US Pat. No. 5,707,668).

Claims 1-34 have been amended, and claims 35 – 47 have been added, the claims pending in the above-identified patent application are Claims 1-47. Claims 1-34 have been amended to more clearly define Applicants' invention. Support for these amendments can be found, for example, in the Claims as originally filed and in the specification at page 7, lines 3-21. Support for new Claims 35-47 can be found, for example, in the Claims as originally filed and in the specification at page 7, lines 11-13, and at page 19, lines 8-13.

In amending the above Claims, Applicants are not acquiescing to the objections or rejections asserted by the Examiner. Applicants have amended the Claims to further

the prosecution of this application and retain the right to file divisional or continuing applications to claim any canceled subject matter.

No new matter has been added by these amendments. Reconsideration and withdrawal of the rejections in light of the preceding amendments and the following remarks are respectfully requested.

Claim Rejections – 35 U.S.C. § 103(a) obviousness

Claims 1-34 are rejected under 35 U.S.C. 103(a) as being obvious over *Dong et al.* (5,770,227) in view of *Patrick et al.* and *Ayer et al.* (US Pat. No. 5,707,668).

With regard to Claims 1-34, this rejection is respectfully traversed. To the extent the rejection may apply to new Claims 35-47, it is also traversed.

Applicants' invention is not *prima facie* obvious from the disclosures of the cited references. In order to be *prima facie* obvious over a combination of references, the references must describe or teach each of the claim limitations and the references must themselves suggest their particular combination and a reason for that combination without reference to Applicants' application. In addition, some suggestion or motivation must be provided to modify the documents to reach the claimed invention. Further, a document must be considered as a whole, including those portions of the document that teach away from the claimed invention. None of the references, either taken alone or in combination, are considered to establish the *prima facie* obviousness of those claims, and the Examiner has not met the burden in properly rejecting the claims.

The Examiner asserts that *Dong et al.* teaches use of progesterone in an extended release delivery system of multi layers for hormone replacement therapy, that *Patrick et al.* teaches the use of methylphenidate in an extended release form, and that *Ayer et al.* teaches the use of anti-epileptic drugs in an extended release form. The above references are asserted to teach a core of antiepileptic drug, a semipermeable wall, wall for pushing the therapeutic composition and an exit, but do not teach an ascending form. The Examiner asserts that one skilled in the art would have been motivated to employ the above references

With respect to claims 1-47, the references do not teach or suggest Claims relating to delivery of a drug from a multiple drug-layer dosage form delivering at a substantially ascending release rate utilizing a longitudinally compressed tablet over a prolonged period of time as claimed by Applicants.

First, *Dong* teaches only a bilayer core dosage form for dispensing a single layer of drug, progesterone, to the gastrointestinal tract of a human. The dosage form contains a progesterone layer and a push layer (Example 7, for example). *Dong* fails to teach or suggest any dosage form containing a tri- or multiple drug-layer formulation as claimed by Applicants. *Dong* relates only to a single drug layer. Moreover, there is no motivation to provide more than a single drug layer as claimed by Applicants. Neither *Patrick*, nor *Ayer* provide any assistance in this regard. None teach or suggest, alone or in combination, a multi drug-layer core as claimed by Applicants.

Accordingly, *Dong* in view of *Patrick* and *Ayer* does not disclose, teach or motivate an osmotic delivery system comprising a multiple drug-layer core as claimed by Applicants.

Second, *Dong* only describes delivering a drug at a constant rate, or approximately zero order rate of release, and not the substantially ascending rate as claimed by Applicants. *Dong* Figures 1-3. *Dong* does not teach or suggest a dosage form that releases drug at an ascending release rate as claimed by Applicants. *Dong* merely provides an "acceptable oral means for administering progesterone at a controlled dose over time," (column 1, lines 46-48).

Similarly, *Ayer* teaches only an approximately zero order rate of release. *Ayer* Figures 6-9. *Ayer* discloses only constant, zero order, rate of release in its Example 1, Col. 13, line1 and teaches away from anything but a zero order rate of release .

Additionally, *Patrick* fails to supply that which is missing from *Dong* and *Ayer,* to disclose or motivate an ascending rate of release. *Patrick* provides a perspective on the absorption of sustained-release methylphenidate formulations compare to immediate release formulations (page 165). However, *Patrick* does not teach, motivate or even address an ascending release rate. *Patrick* compares three products: a 10mg tablet of MPH-IR Ritalin®, a 20 mg tablet of MPH-SR Ritalin®, and a newly formulated 20 mg tablet of MPH-SR from MD Pharmaceuticals (Santa Ana, Ca) (page 166), none of which are ascending release rate profiles.

There simply is no teaching or motivation in the prior art cited by the Examiner to

deliver a drug, much less methylphenidate at a substantially ascending rate of release.

Third, there is no teaching within *Dong* or *Ayer* to suggest utilizing a longitudinally compressed tablet to provide the rate of release, substantially ascending, as claimed by Applicants. As identified by Applicants at page 19, lines 8-13, Applicants' unique longitudinally compressed tablet core configuration ensures that, as the push layer expands longitudinally within the compartment formed by the semipermeable membrane, the surface area of the push layer in contact with the semipermeable membrane is increased more than when other configurations are used, i.e., the standard biconvex tablet shape configuration taught by *Dong* and *Ayer* and utilized in the tablets of *Patrick*.

Applicants respectfully submit that all of the elements recited in Claims 1-47 are not taught or suggested by *Dong*, *Patrick* and *Ayer*. Moreover, Applicants further submit that one of skill in the art at the time of the invention would not have been motivated to prepare a dosage form as recited in Applicants' Claims. The only means for the Examiner to find such motivation would be through improper hindsight, which is not permitted.

Therefore, it would not have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to provide a multi drug-layer dosage form delivering a drug at a substantially ascending release rate utilizing a longitudinally compressed tablet configuration over a prolonged period of time as claimed by Applicants. Contrary to the Examiner's assertion, the art cited does not motivate the

use of a multiple drug-layer delivery system, much less the longitudinally compressed tablet shape claimed by Applicants to obtain the substantially ascending rate of release of the invention.

Furthermore, Applicants' Claims do not claim "another wall for pushing the therapeutic composition" as the Examiner asserts the cited references disclose to obviate Applicants' Claims.

Accordingly, it is submitted that the methods for delivery of drugs at an ascending rate of release, especially of methylphenidate, in Claims 1-47 define a patentable invention. Reconsideration of the application is respectfully requested. Please direct any questions to the undersigned attorney at (650) 564-5171.

The Commissioner is hereby authorized to charge any additional fees associated with this paper or during the pendency of this application, or credit any overpayment, to Deposit Account No. 01-1173.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,
ALZA CORPORATION

Dated: May 8, 2002

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Version with markings to show changes made

In the Claims:

Amend claims 1-34 as follows:

1. (Amended) A method for treating a condition comprising [with a drug indicated for treatment of the said condition, the method comprising the step of] orally administering a longitudinally compressed tablet core dosage form containing a [said] drug in a pharmaceutically acceptable carrier wherein the [said] dosage form releases the [said] drug [from said dosage form] at an ascending release rate for an extended time period.

2. (Amended) A [The] method for administering a drug to a subject [method described in claim 1 wherein said dosage form is an osmotic dosage form] comprising:

administering a dosage from to the subject wherein the dosage form comprises:

(a) a longitudinally compressed tablet core [containing] comprising a plurality of layers wherein the drug is contained in at least one layer and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane [wall] surrounding the said longitudinally compressed tablet core to thereby forming [form] a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the [said] semipermeable membrane [wall] into the [said] compartment; and

(c) an orifice formed through the [said] semipermeable membrane [wall] and into the [said] longitudinally compressed tablet core to permit drug to be released from within the [said] compartment into the [said] external fluid environment;

wherein the dosage form releases the drug at an ascending release rate for extended time period.

3. (Amended) The method according to [described in] claim 2, wherein the [said] longitudinally compressed tablet core comprises two layers and the [said] drug is contained within a first layer and the [said] fluid-expandable polymer is contained within a second layer and [further wherein said] the orifice is formed through the [said] semipermeable membrane [wall at a location] adjacent the [to said] first layer.

4. (Amended) The method according to [described in] claim 3, wherein the [said osmotic] dosage form further [additionally] comprises an outer surface having an immediate-release dose of a drug applied as a coating onto the outer surface of the [said osmotic] dosage form.

5. (Amended) The method according to [described in] claim 2, wherein the [said] longitudinally compressed tablet core comprises three layers and a portion of the [said] drug is contained within a first layer and the remaining portion of the [said] drug is contained within a second layer, wherein the portion [concentration] of drug contained within the [said] first layer is less than the portion [concentration] of drug contained within the [said] second layer, and wherein the [said] fluid-expandable polymer is contained within a third layer and the [said] orifice is formed through the [said] semipermeable membrane [wall at a location] adjacent [to said] the first layer.

6. (Amended) The method according to [described in] claim 5, wherein the [said osmotic] dosage form further [additionally] comprises an immediate-release dose of a drug applied as a coating onto the outer surface of the [said osmotic] dosage form.

7. (Amended) A method for treating ADHD, the method comprising [the step of] orally administering a longitudinally compressed tablet dosage form containing a CNS-acting drug in a pharmaceutically acceptable carrier wherein the [said] dosage form releases the [said] CNS-acting drug from the [said] dosage form at an ascending release rate for an extended time period.

8. (Amended) The method according to [described in] claim 7, wherein the [said] CNS-acting drug is a CNS-stimulant drug selected from the group consisting of methylphenidate, d-threo-methylphenidate, amphetamine, dextroamphetamine, methamphetamine, phenylisopropylamine and pemoline.

9. (Amended) The method according to [described in] claim 8, wherein the [said] CNS-stimulant drug is methylphenidate.

10. (Amended) The method according to [described in] claim 9, wherein the [said] dosage form comprises: [is an osmotic dosage form comprising:]

(a) a longitudinally compressed tablet core containing a plurality of layers wherein methylphenidate is contained in at least one layer and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane [wall] surrounding the [said] longitudinally compressed tablet core to [thereby] form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the [said] semipermeable membrane [wall] into the [said] compartment; and

(c) an orifice formed through the [said] semipermeable membrane [wall] and into the [said] longitudinally compressed tablet core to permit methylphenidate to be released from [within said] the compartment into the [said] external fluid environment.

11. (Amended) The method according to [described in] claim 10, wherein the [said] longitudinally compressed tablet core comprises two layers and the [said] methylphenidate is contained within a first layer and the [said] fluid-expandable polymer is contained within a second layer and further wherein the [said] orifice is formed through the [said] semipermeable membrane [wall] at a location adjacent to the [said] first layer.

12. (Amended) The method according to [described in] claim 11, wherein the [said] osmotic dosage form additionally comprises an immediate-release dose of methylphenidate applied as a coating onto the outer surface of the [said osmotic] dosage form.

13. (Amended) The method according to [described in] claim 10, wherein the [said] longitudinally compressed tablet core comprises three layers and a portion of the [said] methylphenidate is contained within a first layer and the remaining portion of the [said] methylphenidate is contained within a second layer, wherein the portion [concentration] of methylphenidate contained within the [said] first layer is less than the portion [concentration] of methylphenidate contained within the [said] second layer, and wherein the [said] fluid-expandable polymer is contained within a third layer and the [said] orifice is formed through the [said] semipermeable membrane [wall at a location] adjacent the [to said] first layer.

14. (Amended) The method according to [described in] claim 13, wherein the [said osmotic] dosage form further [additionally] comprises an outer surface having an immediate-release dose of methylphenidate applied as a coating onto the outer surface of the [said osmotic] dosage form.

15. (Amended) A method for [effectively] treating ADHD [for a prolonged therapy period of at least about 10 hours] comprising administering [methylphenidate in] a dosage form comprising methylphenidate that provides release of methylphenidate at an ascending release rate over an extended time period.

16. (Amended) A method [for providing plasma methylphenidate concentrations that are substantially smoothly ascending over an extended time period] comprising administering methylphenidate in a longitudinally compressed tablet dosage form that provides release of methylphenidate at an ascending release rate over an extended time period and further provides plasma methylphenidate concentrations that are substantially smoothly ascending over an extended time period.

17. (Amended) A longitudinally compressed tablet dosage form comprising a drug in a pharmaceutically acceptable carrier wherein[, following oral administration, said] the dosage form releases the [said] drug from the [said] dosage form at an ascending release rate for an extended time period following oral administration to a subject.

18. (Amended) A [The] dosage form [described in claim 17 wherein said dosage form is an osmotic dosage form] comprising:

(a) a longitudinally compressed tablet core containing a plurality of layers wherein a [said] drug is contained in at least one layer and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane [wall] surrounding the [said] longitudinally compressed tablet core to [thereby] form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the [said] semipermeable membrane [wall] into the [said] compartment; and

(c) an orifice formed through the [said] semipermeable membrane [wall] and into the [said] longitudinally compressed tablet core to permit the drug to be released from within the [said] compartment and into the [said] external fluid environment.

19. (Amended) The dosage form according to [described in] claim 18, wherein the [said] longitudinally compressed tablet core comprises two layers and the [said] drug is contained within a first layer and the [said] fluid-expandable polymer is contained within a second layer and further wherein the [said] orifice is formed through the [said] semipermeable membrane [wall at a location] adjacent the [to said] first layer.

20. (Amended) The dosage form according to [described in] claim 19, wherein the [said osmotic] dosage form further [additionally] comprises an outer surface having an immediate-release dose of a drug applied as a coating onto the outer surface of said osmotic dosage form.

21. (Amended) The dosage form according to [described in] claim 18, wherein the [said] longitudinally compressed tablet core comprises three layers and a portion of the [said] drug is contained within a first layer and the remaining portion of the [said] drug is contained within a second layer, wherein the portion [concentration] of drug contained within the [said] first layer is less than the portion [concentration] of drug contained within the [said] second layer, and wherein the [said] fluid-expandable polymer is contained within a third layer and the [said] orifice is formed through said semipermeable membrane [wall at a location] adjacent the [to said] first layer.

22. (Amended) The dosage form according to [described in] claim 21, wherein the [said osmotic] dosage form additionally comprises an outer surface having an

immediate-release dose of a drug applied as a coating onto the outer surface of the [said] osmotic dosage form.

23. (Amended) A longitudinally compressed tablet dosage form containing a CNS-acting drug in a pharmaceutically acceptable carrier wherein the [said] dosage form, following oral administration to a subject, releases the [said] CNS-acting drug from the [said] dosage form at an ascending release rate for an extended time period.

24. (Amended) The dosage form according to [described in] claim 23, wherein the [said] CNS-acting drug is a CNS-stimulant drug selected from the group consisting of methylphenidate, d-threo-methylphenidate, amphetamine, dextroamphetamine, methamphetamine, phenylisopropylamine and pemoline.

25. (Amended) The dosage form according to [described in] claim 24, wherein the [said] CNS-stimulant drug is methylphenidate.

26. (Amended) The dosage form according to [described in] claim 25 [wherein the said dosage form is an osmotic dosage form] comprising:

(a) a longitudinally compressed tablet core containing a plurality of layers wherein methylphenidate is contained in at least one layer and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane [wall] surrounding the [said] longitudinally compressed tablet core to [thereby] form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the [said] semipermeable membrane [wall] into the [said] compartment; and

(c) an orifice formed through the [said] semipermeable membrane [wall] and into the [said] longitudinally compressed tablet core to permit

methylphenidate to be released from within the [said] compartment into the [said] external fluid environment.

27. (Amended) The dosage form according to [described in] claim 26, wherein the [said] longitudinally compressed tablet core comprises two layers and the [said] methylphenidate is contained within a first layer and said fluid-expandable polymer is contained within a second layer and further wherein the [said] orifice is formed through the [said] semipermeable membrane [wall at a location] adjacent the [to said] first layer.

28. (Amended) The dosage form according to [described in] claim 27, wherein the [said osmotic] dosage form further [additionally] comprises an outer surface having an immediate-release dose of methylphenidate applied as a coating onto the outer surface of the [said osmotic] dosage form.

29. (Amended) The dosage form according to [described in] claim 26, wherein the [said] longitudinally compressed tablet core comprises three layers and a portion of the [said] methylphenidate is contained within a first layer and the remaining portion of the [said] methylphenidate is contained within a second layer, wherein the portion [concentration] of methylphenidate contained within the [said] first layer is less than the portion [concentration] of methylphenidate contained within the [said] second layer, and wherein the [said] fluid-expandable polymer is contained within a third layer and the [said] orifice is formed through the [said] semipermeable membrane [wall at a location] adjacent the [to said] first layer.

30. (Amended) The dosage form according to [described in] claim 29, wherein the [said osmotic] dosage form further [additionally] comprises an outer surface having an immediate-release dose of methylphenidate applied as a coating onto the outer surface of the [said osmotic] dosage form.

31. (Amended) The dosage form according to [described in] claim 30, wherein the [said] coating comprises an antidegradation agent.

32. (Amended) The dosage form according to [described in] claim 31, wherein the [said] antidegradation agent is phosphoric acid.

33. (Amended) The dosage form according to [described in] claim 29, wherein the [said] semipermeable membrane comprises cellulose acetate and a flux-enhancing agent.

34. (Amended) The dosage form according to [described in] claim 33, wherein the [said] flux-enhancing agent is a copolymer of ethylene and propylene oxide.

Please add claims 35- 47 as follows:

35. (New) An oral dosage form comprising a drug and a pharmaceutically acceptable carrier comprising:

(a) a capsule shaped osmotically active tablet core comprising at least one drug containing layer and a push layer wherein the push layer comprises a suitable fluid expandable polymer;

(b) a semipermeable membrane surrounding the capsule shaped osmotically active tablet core to form a compartment; and

(c) an orifice formed through the semipermeable membrane and into the capsule shaped osmotically active tablet core at a location adjacent the at

least one drug layer to permit the drug to be released from within the compartment into the external fluid environment in response to osmotic passage of fluid into the capsule shaped osmotically active tablet core, wherein the dosage form releases the drug at an ascending release rate for an extended time period.

36. (New) The dosage form according to claim 35, wherein the dosage form further comprises a drug layer overcoat.

37. (New) The dosage form according to claim 35, wherein the push layer further comprises at least one osmagent.

38. (New) The dosage form according to claim 35, wherein the dosage form is a bi-layer dosage form comprising one drug layer and a push layer.

39. (New) The dosage form according to claim 38, wherein the bi-layer dosage form achieves an ascending release rate for an extended time period of at least 50% of a T_{90} period.

40. (New) The dosage form according to claim 38, wherein at least about 35% of the push layer comprises the osmagent.

41. (New) The dosage form according to claim 40, wherein the osmagent is sodium chloride.

42. (New) The dosage form according to claim 38, wherein the dosage form further comprises an outer surface and an immediate-release dosage of the drug applied as a coating onto the outer surface.

43. (New) The dosage form according to claim 38, wherein the drug layer comprises methylphenidate or a pharmaceutically acceptable salt thereof.

44. (New) The dosage form according to claim 40, wherein the coating comprises an antidegradation agent.

45. (New) The dosage form according to claim 44, wherein the antidegradation agent is phosphoric acid.

46. (New) The dosage form according to claim 43, wherein the semipermeable membrane further comprises cellulose acetate and a flux-enhancing agent.

47. (New) The dosage form according to claim 46, wherein the flux-enhancing agent is a copolymer of ethylene and propylene oxide.